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Dexmedetomidine sedation for endobronchial ultrasound-guided transbronchial needle aspiration, a randomized controlled trial

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Compared to propofol sedation for EBUS-TBNA, dexmedetomidine provided patients lighter sedation with lower heart rates and a less decrease in blood pressure. The recovery times, hypoxemia, cooperation and diagnostic yield in the two groups were similar.

Abstract

Background and aim: Appropriate sedation is important to the success of endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA). Dexmedetomidine is a sedative agent that operates via the α2 adrenergic agonist, which provides sleep-like sedation with little respiratory suppression. The study compared the efficacy and safety of dexmedetomidine sedation with propofol in cases of EBUS-TBNA.

Methods: Patients requiring EBUS-TBNA were randomly assigned dexmedetomidine sedation (D, n=25) or propofol sedation (P, n=25). Vital signs, diagnostic yield, and the bispectral index (BIS) were recorded throughout the bronchoscopic procedure and recovery period. The tolerance and cooperation of the patients were evaluated using questionnaires.

Measurements and Results: The lowest mean arterial blood pressure in group D (79.2±9.9 vs. 72.5±12.9mmHg, p=0.049) exceeded that in group P, the lowest heart rate was lower (60.9±10.2 vs. 71.4±11.8 beat/min, p=0.006) and the mean BIS during sedation was significant higher (84.1±8.3 vs. 73.6±5.7, p<0.001). Patients in group D were more likely to report perceiving procedure-related symptoms and express an unwillingness to undergo the bronchoscopy again, if indicated (41.1 vs. 83.3%, p=0.007). One subject in group D aborted EBUS-TBNA due to intolerance. Many of the variables in the two groups were similar, including the proportion of hypoxemic event, recovery times, patient cooperation, and diagnostic yield.

Conclusions: The effects of dexmedetomidine on hemodynamics was in line with its pharmacodynamic features. Patients who received dexmedetomidine were more likely than those who received propofol to perceive the procedures. Overall, dexmedetomidine did not prove inferior to propofol sedation in terms of patient cooperation or diagnostic yield.

Introduction

Endobronchial ultrasound (EBUS)-guided transbronchial needle aspiration (TBNA) is an essential procedure for lung cancer diagnosis and staging. Sampling mediastinal lymph nodes using EBUS-TBNA is far easier than conventional mediastinoscopy [1]. Note that this procedure is performed orally and multiple sampling is required. Note also that performing additional procedures, such as endobronchial or transbronchial lung biopsy, can greatly prolong the duration of the procedure. Under these conditions, appropriate sedation is essential to assuring patient cooperation and minimizing patient discomfort throughout the entire procedure [2-4].

Propofol sedation is ideally suited to flexible bronchoscopy, due to its rapid onset and short-term effects [5] [6, 7]. Propofol acts mainly through GABA receptor potentiation. It tends to decrease the central respiratory drive as well as pharyngeal muscle tone [8-11]. Physicians overseeing propofol sedation should undergo training specifically for this drug. Target-controlled infusion (TCI) and bispectral index (BIS) monitors are commonly used to prevent cardiopulmonary depression due to oversedation [12-16]. Despite a growing body of evidence supporting the efficacy and safety of propofol, the use of this drug for procedural sedation by non-anesthesiologists is limited in many countries [17]. Midazolam, is the standard alternative to propofol sedation; however, further options, such as dexmedetomidine, should also be explored.

Dexmedetomidine has been approved in the Europe and United State for its sedative and analgesic effects. The effects are exerted via α2 adrenergic receptors in the locus coeruleus and dorsal horn of the spinal cord. The fact that dexmedetomidine has relatively little effect on muscles of the upper airway greatly limits respiratory depression during sedation [18-22]. Among the cardiovascular effects is a decrease in the heart rate and blood pressure within hours of infusion [23].

Dexmedetomidine induces sleep-like sedation, from which the patient is easy aroused. The patients also tend to be more cooperative and display better cognitive function [24, 25].

Our aim in this study was to compare the effectiveness of dexmedetomidine and propofol for EBUS-TBNA in terms of cardiopulmonary parameters, patient tolerance, cooperation, and diagnostic yield. For those area where pulmonologists could not perform propofol sedation, (for example due to legislative requirements) the current study would like to explore if an alternative opinion for sedation of EBUS-TBNA if propofol cannot be used. Because plenty studies have compared midazolam to propofol, we choice dexmedetomidine, which pulmonologists can use for sedation of patients with mechanical ventilation in current practice. Meanwhile, there is no any previous study to show the EBUS-TBNA diagnostic yield and detailed sedative profiles among patients undergoing dexmedetomidine. Therefore, we conducted this prospective study to provide the pulmonologists scientific evidence of the role of dexmedetomidine in EBUS-TBNA sedation. Some of the results have been published in ERS international congress 2019 [26]

Methods

This prospective, open-labelled, randomized study was conducted in a medical center (Chang-Gung Memorial Hospital, Linkou, Taiwan). The study protocol was approved by the Chang Gung Medical Foundation Institutional Review Board (No.201601093A3). The trial was registered at clinicaltrials.gov (NCT03521505). Patients who required EBUS-TBNA and agreed to undergoing the procedure under sedation were screened for enrolment. The exclusion criteria included age <20 years, American Society of Anaesthesiologists (ASA) physical status classification 4 or 5, a Mallampati score of 4, severe sleep apnoea syndrome (apnoea-hypopnea index >40), second or third degree atrioventricular blockage, heart rate <50 beats per minute, systolic blood pressure <90mmHg, neurologic disorders or other conditions contributing to difficulty in assessing response, body mass index >42 in males or >35 in females, and pregnancy. Patients with a known history of allergy to the study drugs, or to eggs, soybeans, or sulfite products, were also excluded. All enrolled patients

provided written informed consent. Enrolled patients were randomised using a predetermined random computer code into the study group or the control group at a ratio of 1:1.

Patient preparation

Blood pressure was monitored using an automated pressure cuff, and heart rate (HR) was monitored using a three-lead electrocardiograph (ECG). A peripheral pulse oximeter was used to monitor oxyhemoglobin saturation (SpO_2), while a nasal cannula delivered oxygens at rate of 2 L/min. A disposable BIS Quatro Sensor (Aspect Medical System Inc, Newton, MA, USA) was applied to the forehead of patients. Smoothening time was set at 15 s[12]. The BIS level was covered (i.e., blinded to the investigator in charge of sedation). A patient monitor (Philips MP60) was used to continuously record all parameters except for the blood pressure, which was recorded every 2.5 minutes. The monitoring software was developed in Microsoft Visual Basic 6.0 (Windows XP) based on the Philip Patient Monitor communication protocol. An intravenous catheter was placed in the forearm for drug administration. An oral bite block was placed prior to sedation. Pre-medication was achieved using nebulized 2% xylocaine inhalation.

The investigators in charge of sedation were specifically trained in the administration of sedatives and monitoring sedative depth [12, 13, 15, 27-29]. In our hospital, physicians who operate procedure sedation must receive the training lesson about how to monitor the sedative depth, the pharmacology of sedative drugs, the risk assessments for sedation. The lesson is in charged by the anesthesiologists and participants have to take the lesson and pass the test every two years. They were responsible for monitoring patients for cardiopulmonary depression and determining the need for interventions. The interventions are detailed in the supplemental materials. EBUS-TBNA operations were performed by experienced bronchoscopists (Kuo C-H and Chung F-T) using a convex probe endobronchial ultrasound (BF-UC260FW, Olympus, Tokyo, Japan). via the oral route, with assistance from a well-trained technician.

Sedation protocol

Study group: Alfentanil (5 μg/kg) was administered in a 1:10 dilution with normal saline under slow injection for 2 min prior to full induction using an infusion of dexmedetomidine (1μg/kg) for 10 min [18, 22, 30]. Maintenance was conducted via dexmedetomidine infusion (0.5~1.4 μg/kg/hour) with the aim of maintaining stable vital signs and The Observer Assessment of Alertness and Sedation scale (OAA/S) of 3~2.

Control group: Patients were slowly administered alfentanil (5 μg/kg) in a 1:10 dilution with normal saline for 2 min prior to induction using a propofol infusion at an initial effect-site concentration (Ce) of 2.0μg/ml using a Injectomat^{R} TIVA Agilia, (Fresenius Kabi, France)[11, 13]. OAA/S was evaluated every 30 s after the patients closed their eyes. In cases where OAA/S did not reach 3 when Ce reached 2.0 μg/ml, Ce was increased by 0.2μg/ml every 90 seconds until OAA/S reached 3~2. Maintenance of control group: Ce of propofol was titrated at a rate of 0.2μg/ml every 90 seconds to achieve stable vital signs and The Observer Assessment of Alertness and Sedation scale (OAA/S) 3~2.

Following the procedure, the patients were monitored continuously in a recovery room until full recovery.

Assessment

SPO_2, blood pressure, HR, and BIS were recorded immediately before induction (as a baseline), during induction, during the maintenance of sedation, and throughout the recovery period. The parameter levels and the difference from the baseline values were analysed. We recorded episodes of hypoxemia (SpO_2<90%) and hypotension (mean arterial blood pressure (MAP) <65 mmHg or systolic blood pressure (SBP) <90 mmHg) of any duration. Sedative drug doses were recorded at the infusion pump. Procedure time was recorded as the duration from the insertion of bronchoscope to its removal. Recovery time was recorded as the duration between the time at which bronchoscopy

finished and the time when the patients spontaneously opened their eyes and were able to recall their date of birth and correctly perform the finger-to-nose test.

After recovery, patients were asked to answer questionnaire about wakefulness, tolerance, and willingness to repeat the bronchoscopic procedure if clinically indicated. Wakefulness during the procedure was evaluated by asking patients if they heard or saw anything during the operation. The questionnaire used to assess patient tolerance to procedure-related symptoms included reactions to nebulized xylocaine inhalation, stimulation caused by insertion of the scope through the mouth, cough, dyspnea, pain, and global discomfort to the entire procedure. The questionnaire used a 100-mm visual analogue scale (VAS, 0: no bother, 100: intolerable). Patients were also asked about their willingness to undergo the bronchoscopic procedure again if clinically indicated (definitely not, possibly not, not sure, possibly yes and definitely yes). The bronchoscopist was questioned concerning the ease of scope insertion and biopsy, coughing by the patient, and global cooperation throughout the procedure using a 100-mm VAS (0: most cooperative, 100: entirely uncooperative).

The diagnostic yield of EBUS-TBNA was evaluated in terms of the pathology or cytology of mediastinal lymph nodes. Specimens without lymphocytes were defined as inadequate samples. There are two criteria by which to confirm a result as a true negative. The first is confirming a lack of malignancy in specimens obtained surgically. The second is a confirmation of stability or regression via computed tomography at 6 months after the procedure [31].

Sample size

Power calculations were based on the proportion of patients with at least one episode of hypoxemia during sedation of bronchoscopy. Among the patients who underwent bronchoscopy, 3% of those under dexmedetomidine sedation and 36.7% of those under propofol sedation experienced episodes of hypoxemia [13, 18, 22]. Considering the complexity of EBUS-TBNA, a difference of 30% would be

of clinical importance (α=0.05, power=0.8). Our analysis revealed that 25 subjects per group would be sufficient to detect a difference between the two groups.

Statistical analysis

Analysis was performed on the outcomes of all randomized subjects. The diagnostic yield among subjects who completed EBUS-TBNA was expressed as a number with a percentage or a mean with standard deviation. Ccontinuous variables were evaluated using the Mann-Whitney test. Patient characteristics and complications were analysed using the Chi-square test or Fisher's exact test, in cases where the sample size was small. A $p<0.05$ was considered statistically significant. All the statistical analysis was performed using Prism 5 (GraphPad software Inc., San Diego, CA, USA).

Results

Baseline characteristics

The trial was conducted from May 2018 through January 2020. Five subjects who declined to join the study during the screening phase were excluded. The remaining 50 subjects were randomly assigned dexmedetomidine or propofol for sedation. Both groups presented comparable patient characteristics and indications, and the add-on procedures in the two groups were similar (Table 1). The main add-on procedures were mini-probe endobronchial ultrasound and transbronchial lung biopsy. Baseline blood pressure, HR, SPO_2, and BIS levels were comparable in the two groups (Table S1 in the Supplemental Materials). One subject who underwent dexmedetomidine sedation was unable to complete EBUS-TBNA due to intolerance.

Table 1. Patient characteristics, bronchoscopic procedures performed, and doses of sedative drugs in the two groups

	Dexmedetomidine (n=	Propofol (n =25)	p value

	25)		
Patient characteristics			
Age (SD), yr	59.7 (14.1)	59.4 (12.2)	0.9
ASA (Median with range)	3 (1-3)	3 (1-3)	0.7
Male, n (%)	14 (56.0)	13 (52.0)	1.0
Body mass index (SD)	23.6 (3.9)	23.6 (3.8)	0.8
Mallampati score (Median with range)	2 (1-3)	2 (1-3)	0.5
Intolerance and withdrawal, n (%)	1 (7.0)	0	1.0
Procedure time#, min	30.0 (13.2)	27.6 (8.6)	0.7
Add-on procedures			
Mini-probe endobronchial ultrasound, n (%)	16 (64.0)	12 (48.0)	0.4
Transbronchial lung biopsy, n, (%)	12 (48.0)	11 (44.0)	1.0
Bronchial wash	13 (52.0)	11(44.0)	0.8
Bronchioalveolar larvae	3 (12.0)	4 (16.0)	1.0

Total doses of sedatives, mg	95.6 (29.5)	184.1 (64.4)	-
Recovery time§, min	12.4 (11.1)	6.2 (4.8)	0.06

Procedure time: duration from the insertion of bronchoscope to its removal.

§ Recovery time: duration between the time of finishing bronchoscopic procedure and the time when the patients could spontaneously open their eyes, recall their date of birth, and correctly perform the finger-to-nose test.

During induction (Table S2 in the Supplemental Materials), the incidence of hypoxemia and hypotension was similar in the two groups. HR in the dexmedetomidine group was significantly lower than in the propofol group. BIS level in the propofol group were lower than in the dexmedetomidine group.

During maintenance (Table 2), blood pressure and BIS levels in the dexmedetomidine group was significantly higher than in the propofol group, whereas heart rates were lower. The incidence of hypoxemia was similar in the two groups. All of the patients that presented hypoxemia or hypotension recovered spontaneously under proper management. There were no occurrences of intubation, mortality, or severe bleeding. During the recovery period, the effects of sedative drugs on vital signs vanished in both groups; however, HR in the dexmedetomidine group remained lower than in the propofol group (Table S3 in the Supplemental Materials).

Table 2 Hemodynamics in the two groups during the period of maintenance*

Events	Dexmedetomidine (n= 25)	Propofol (n =25)	p value
Blood pressure, mmHg			

Lowest MAP	79.2 (9.9)	72.5 (12.9)	0.04
△MAP†	-16.7 (13.8)	-21.9 (13.6)	0.1
MAP<65mmHg, n (%)	1 (4.0)	5 (20.0)	0.2
Lowest SBP	106.7 (13.8)	98.2 (13.4)	0.049
△SBP†	-24.9 (15.7)	-36.0 (23.2)	0.1
SBP<90mmHg, n (%)	3 (12.0)	7 (28.0)	0.3
Heart rate, beats/min			
Lowest heart rate	60.9 (10.2)	71.4 (11.8)	0.006
△heart rate†	-13.6 (9.3)	-3.3 (9.1)	<0.001
Heart rate<60/min, n (%)	12 (48.0)	4 (16.0)	0.03
Oxygenation, %			
Lowest SPO2	90.9 (5.2)	87.9 (6.3)	0.1
△SPO2†	-8.3 (5.3)	-10.9 (6.2)	0.1
SPO2<90%, n (%)	8 (32.0)	14 (56.0)	0.2
Mean BIS	84.1 (8.3)	73.6 (5.7)	<0.001

Data are presented as number and percentage or mean with standard deviation

*Duration from insertion of bronchoscope to withdraw

Abbreviations: MAP: mean arterial pressure; SBP: systolic blood pressure; SpO2: oxyhemoglobin saturation; BIS: bispectral index; EMG: electromyography.

†△ is defined as the difference between the lowest level of vital signs during the period of bronchoscopic procedures and that before induction.

Following recovery, one subject in each of the groups refused to answer the questionnaire, such that 48 patients were evaluated for wakefulness during bronchoscopy, patient tolerance, and willingness to undergo the procedure again. Patients in the dexmedetomidine group were more likely to report wakefulness than were those in the propofol group (Figure 1). Patients in the dexmedetomidine group were also more likely to report hearing something (58.3 vs 16.7%, p=0.007) or seeing something (20.8 vs 4.2%, p=0.2) while under sedation. In terms of tolerance, patients in the dexmedetomidine group were more likely to perceive procedure-related symptoms, as indicated by VAS values (Figure2A). The proportion of patients that unreservedly agreed to repeated bronchoscopy (if indicated) was higher in the propofol group than in the dexmedetomidine group (41.1% vs 83.3%, p=0.007, Figure 3). The attending bronchoscopists reported that patient cooperation and ease of biopsy during bronchoscope insertion as well as coughing by the patient were similar in the two groups.

Samples adequate for pathological examination were obtained from patients in both groups: dexmedetomidine group (29 nodes) and propofol group (32 nodes). Three nodes from one patient in the propofol group were excluded from analysis because the patient was lost from follow-up, such that negative nodal biopsy results could not be judged as a true negative (Table 3). The diagnostic yield was comparable in the two groups in terms of true positive rate (48.3% vs 37.9%), true negative rate (48.3% vs 48.3%) and false negative rate (3.4% vs 13.8%).

Table 3. Diagnostic yield of endobronchial ultrasound–guided transbronchial needle aspiration in the two groups

	Dexmedetomidine	Propofol[#]	p value
Lymph node numbers	29	32	
Lymph node station			
7	11	13	
4	8	11	
2	1	1	
10	5	5	
11	4	2	
Adequate nodal number for pathology,	29	32	
Diagnostic yield[#]			
True positive, n (%)	14 (48.3)	11 (37.9)	0.6
Malignancy	13	8	
Sarcoidosis	1	2,1=3	
True negative, n (%)	14 (48.3)	14 (48.3)	1.0
False negative, n (%)	1 (3.4)	4 (13.8)	0.4
Malignancy	1	2	
Sarcoidosis	0	1	
Thyroid nodal hyperplasia	0	1	

The 3 nodes from one patient in the propofol group were excluded from analysis of diagnostic yield because the patient was lost from follow-up, such that negative nodal biopsy results could not be judged as a true negative

Discussion

Our results revealed that compared to patients that underwent propofol sedation for EBUS-TBNA, those who underwent dexmedetomidine sedation experienced lighter sedation with lower heart rates and a less pronounced decrease in blood pressure. Note that recovery times and the incidence of hypoxemia in the two groups were similar. No severe complications were encountered in either group. Patients in the dexmedetomidine group were more likely to perceive procedure-related symptoms and were less likely to express a willingness to repeat the procedure if indicated. Patients in the both groups displayed similar degrees of cooperation during EBUS-TBNA and similar diagnostic yield.

The beneficial effects of dexmedetomidine in terms of respiratory depression did not transfer to oxygenation outcomes in the present study. This may be due to the availability of supplemental O_2

from a nasal cannula for safety. This also implies that the factors contributing to hypoxemia during EBUS-TBNA are multifactorial, such that they could not be improved by a single drug. It appears that procedure-related secretion, coughing, individual cardiopulmonary capacity, and drug metabolization are also possible factors. The study results confirmed our expectations based on the pharmacokinetic features of the drugs that HR in the dexmedetomidine group would be lower than in the propofol group and BP would be higher. Li et al. reported the clinical efficacy of combination of dexmedetomidine and propofol for general anesthesia and compared it with propofol alone for bronchoscopy[32]. The stress index and required propofol doses were less in the group receiving the combination of dexmedetomidine and propofol. Like the present study, the intraoperative heart rate was lower in the patients receiving dexmedetomidine. This study demonstrated the advantage of combining dexmedetomidine in bronchoscopic sedation. However, laryngeal mask was required to maintain adequate ventilation during general anesthesia. Cases of severe bradycardia and cardiac arrest have previously been linked to dexmedetomidine sedation when used for other procedures or as a general anesthesia [33, 34]. In the current study, the mean HR of patients who received dexmedetomidine was 18% below the baseline during maintenance and 13% lower during recovery; however, none of the patients required further intervention to correct this (Table 2 and Table S2). Patients presenting a risk of bradycardia were excluded during screening, and sedation was limited to the dose at which the patient achieved the desired sedative level. Full recovery was confirmed before the patients left the room in which the bronchoscopic procedure was performed.

Based on the BIS levels, we determined that the sedation induced by dexmedetomidine was lighter than that induced by propofol. This difference could be attributed to the properties of the drugs as well as the sedation protocol. Lighter sedation may explain why patients in the dexmedetomidine group were more likely to perceive the procedure and were less likely to express a willingness to undergo the procedure again. Nonetheless, the less pronounced amnesia effects of dexmedetomidine should be taken into consideration when dealing with patients who are subject to high anxiety. Radek et al. also showed patients receiving dexmedetomidine had greater awareness

than patients receiving propofol, which is consistent with our finding.[35]. Thus, it is crucial that physicians explain the contingencies of EBUS-TBNA under sedation. Note that the bronchoscopists assigned similar grades for patient cooperation and diagnostic yield in the two groups. One patient who received dexmedetomidine was unable to tolerate the procedure. Note that dexmedetomidine is not indicated for patients experiencing profound anxiety such that an alternative regimen should be administered. Further studies should be conducted to determine the feasibility of using a low dose of midazolam as premedication prior to the administration of dexmedetomidine [36]. Based on the results obtained in this study, we will undertake a pharmacodynamic study on the use of dexmedetomidine titration to improve amnesia effects and overcome the effects of suppressed cardiopulmonary function.

Most previous studies on the use of sedation for EBUS-TBNA focused on the diagnostic yield. All but one retrospective studies reported that diagnostic yield and patient tolerance under deep propofol sedation was equivalent to that under moderate midazolam sedation [37-40]. Prospective randomized control trials comparing the use of propofol for general anesthesia and midazolam for moderate sedation were also comparable in terms of diagnostic yield, major complications, and patient tolerance [31, 41]. In the current study, we compared the diagnostic yield and detailed sedative profiles among patients undergoing dexmedetomidine or propofol sedation from the perspective of patients, bronchoscopists, and physicians overseeing sedation. The information obtained in this study could help to improve patient selection for EBUS-TBNA under sedation.

The present study has a number of limitations. First, we did not exclude cases where procedures other than EBUS-TBNA were performed, as was done in other prospective trials [31, 41]. Thus, this study encountered many situations that arise in real-world practice. Note also that the add-on procedures and procedure duration were equally distributed in the two groups. Second, the investigators in charge of sedation were not blinded to the patients' titration regimen. Nonetheless, the safety profiles of the sedative drugs were in line with their pharmacodynamic features.

Furthermore, the patients reported their own feelings related to the effects of sedation, which is important to real-life practice. Third, because the number of subjects was small, a large-scale study is needed to confirm the results of the present study.

Compared to propofol sedation for EBUS-TBNA, dexmedetomidine resulted in lighter sedation, a more pronounced reduction in heart rate, and less pronounced reduction in blood pressure. The incidence of hypoxemia and the time required for recovery were similar in the two groups. Overall, dexmedetomidine did not prove inferior to propofol sedation in terms of patient cooperation or diagnostic yield.

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No conflict of interest to declare.

References

1. Silvestri GA, Gonzalez AV, Jantz MA, Margolis ML, Gould MK, Tanoue LT, Harris LJ, Detterbeck FC. Methods for staging non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2013: 143(5 Suppl): e211S-e250S.
2. Canneto B, Ferraroli G, Falezza G, Infante MV. Ideal conditions to perform EBUS-TBNA. *J Thorac Dis* 2017: 9(Suppl 5): S414-S417.
3. Aswanetmanee P, Limsuwat C, Kabach M, Alraiyes AH, Kheir F. The role of sedation in endobronchial ultrasound-guided transbronchial needle aspiration: Systematic review. *Endosc Ultrasound* 2016: 5(5): 300-306.
4. Wahidi MM, Sterman DH. Bringing comfort to endobronchial ultrasound bronchoscopy. *Am J Respir Crit Care Med* 2015: 191(7): 727-728.
5. Stolz D, Kurer G, Meyer A, Chhajed PN, Pflimlin E, Strobel W, Tamm M. Propofol versus combined sedation in flexible bronchoscopy: a randomised non-inferiority trial. *Eur Respir J* 2009: 34(5): 1024-1030.
6. Clarkson K, Power CK, O'Connell F, Pathmakanthan S, Burke CM. A comparative evaluation of propofol and midazolam as sedative agents in fiberoptic bronchoscopy. *Chest* 1993: 104(4): 1029-1031.
7. Crawford M, Pollock J, Anderson K, Glavin RJ, MacIntyre D, Vernon D. Comparison of midazolam with propofol for sedation in outpatient bronchoscopy. *Br J Anaesth* 1993: 70(4): 419-422.
8. Murphy M, Bruno MA, Riedner BA, Boveroux P, Noirhomme Q, Landsness EC, Brichant JF, Phillips C, Massimini M, Laureys S, Tononi G, Boly M. Propofol anesthesia and

sleep: a high-density EEG study. *Sleep* 2011: 34(3): 283-291A.
9. Hillman DR, Walsh JH, Maddison KJ, Platt PR, Kirkness JP, Noffsinger WJ, Eastwood PR. Evolution of changes in upper airway collapsibility during slow induction of anesthesia with propofol. *Anesthesiology* 2009: 111(1): 63-71.
10. Eastwood PR, Platt PR, Shepherd K, Maddison K, Hillman DR. Collapsibility of the upper airway at different concentrations of propofol anesthesia. *Anesthesiology* 2005: 103(3): 470-477.
11. Lin T-Y, Fang Y-F, Huang S-H, Wang T-Y, Kuo C-H, Wu H-T, Kuo H-P, Lo Y-L. Capnography monitoring the hypoventilation during the induction of bronchoscopic sedation: A randomized controlled trial. *Scientific Reports* 2017: 7(1): 8685.
12. Lo YL, Lin TY, Fang YF, Wang TY, Chen HC, Chou CL, Chung FT, Kuo CH, Feng PH, Liu CY, Kuo HP. Feasibility of bispectral index-guided propofol infusion for flexible bronchoscopy sedation: a randomized controlled trial. *PLoS One* 2011: 6(11): e27769.
13. Lin TY, Lo YL, Hsieh CH, Ni YL, Wang TY, Lin HC, Wang CH, Yu CT, Kuo HP. The potential regimen of target-controlled infusion of propofol in flexible bronchoscopy sedation: a randomized controlled trial. *PLoS One* 2013: 8(4): e62744.
14. Clark G, Licker M, Younossian AB, Soccal PM, Frey JG, Rochat T, Diaper J, Bridevaux PO, Tschopp JM. Titrated sedation with propofol or midazolam for flexible bronchoscopy: a randomised trial. *Eur Respir J* 2009: 34(6): 1277-1283.
15. American Society of Anesthesiologists Task Force on S, Analgesia by N-A. Practice guidelines for sedation and analgesia by non-anesthesiologists. *Anesthesiology* 2002: 96(4): 1004-1017.
16. Wahidi MM, Jain P, Jantz M, Lee P, Mackensen GB, Barbour SY, Lamb C, Silvestri GA. American College of Chest Physicians consensus statement on the use of topical anesthesia, analgesia, and sedation during flexible bronchoscopy in adult patients. *Chest* 2011: 140(5): 1342-1350.
17. Perel A. Non-anaesthesiologists should not be allowed to administer propofol for procedural sedation: a Consensus Statement of 21 European National Societies of Anaesthesia. *Eur J Anaesthesiol* 2011: 28(8): 580-584.
18. Yuan F, Fu H, Yang P, Sun K, Wu S, Lv M, Dong Z, Dong T. Dexmedetomidine-fentanyl versus propofol-fentanyl in flexible bronchoscopy: A randomized study. *Exp Ther Med* 2016: 12(1): 506-512.
19. Goneppanavar U, Magazine R, Periyadka Janardhana B, Krishna Achar S. Intravenous Dexmedetomidine Provides Superior Patient Comfort and Tolerance Compared to Intravenous Midazolam in Patients Undergoing Flexible Bronchoscopy. *Pulm Med* 2015: 2015: 727530.
20. Ehsan Z, Mahmoud M, Shott SR, Amin RS, Ishman SL. The effects of anesthesia and opioids on the upper airway: A systematic review. *Laryngoscope* 2016: 126(1): 270-284.
21. Venn RM, Hell J, Grounds RM. Respiratory effects of dexmedetomidine in the surgical patient requiring intensive care. *Crit Care* 2000: 4(5): 302-308.
22. Ryu JH, Lee SW, Lee JH, Lee EH, Do SH, Kim CS. Randomized double-blind study of remifentanil and dexmedetomidine for flexible bronchoscopy. *Br J Anaesth* 2012: 108(3): 503-511.
23. Shehabi Y, Ruettimann U, Adamson H, Innes R, Ickeringill M. Dexmedetomidine infusion for more than 24 hours in critically ill patients: sedative and cardiovascular effects. *Intensive Care Med* 2004: 30(12): 2188-2196.
24. Venn RM, Grounds RM. Comparison between dexmedetomidine and propofol for sedation in the intensive care unit: patient and clinician perceptions. *Br J Anaesth* 2001: 87(5): 684-690.
25. Nelson LE, Lu J, Guo T, Saper CB, Franks NP, Maze M. The alpha2-adrenoceptor

agonist dexmedetomidine converges on an endogenous sleep-promoting pathway to exert its sedative effects. *Anesthesiology* 2003: 98(2): 428-436.
26. Lin T-Y, Kuo C-H, Chung F-T, Lo Y-L. Comparison of dexmedetomidine to propofol for sedation of endobronchial ultrasound-guided transbronchial needle aspiration. *European Respiratory Journal* 2019: 54(suppl 63): PA320.
27. Jose RJ, Shaefi S, Navani N. Sedation for flexible bronchoscopy: current and emerging evidence. *Eur Respir Rev* 2013: 22(128): 106-116.
28. Ni YL, Lo YL, Lin TY, Fang YF, Kuo HP. Conscious sedation reduces patient discomfort and improves satisfaction in flexible bronchoscopy. *Chang Gung Med J* 2010: 33(4): 443-452.
29. Fanning RM. Monitoring during sedation given by non-anaesthetic doctors. *Anaesthesia* 2008: 63(4): 370-374.
30. Conti G, Ranieri VM, Costa R, Garratt C, Wighton A, Spinazzola G, Urbino R, Mascia L, Ferrone G, Pohjanjousi P, Ferreyra G, Antonelli M. Effects of dexmedetomidine and propofol on patient-ventilator interaction in difficult-to-wean, mechanically ventilated patients: a prospective, open-label, randomised, multicentre study. *Crit Care* 2016: 20(1): 206.
31. Casal RF, Lazarus DR, Kuhl K, Nogueras-Gonzalez G, Perusich S, Green LK, Ost DE, Sarkiss M, Jimenez CA, Eapen GA, Morice RC, Cornwell L, Austria S, Sharafkanneh A, Rumbaut RE, Grosu H, Kheradmand F. Randomized trial of endobronchial ultrasound-guided transbronchial needle aspiration under general anesthesia versus moderate sedation. *Am J Respir Crit Care Med* 2015: 191(7): 796-803.
32. Li H, Zhang N, Zhang K, Wei Y. Observation of the clinical efficacy of dexmedetomidine in flexible bronchoscopy under general anesthesia: clinical case experience exchange. *J Int Med Res* 2019: 47(12): 6215-6222.
33. Ingersoll-Weng E, Manecke GR, Jr., Thistlethwaite PA. Dexmedetomidine and cardiac arrest. *Anesthesiology* 2004: 100(3): 738-739.
34. Gerlach AT, Murphy CV. Dexmedetomidine-associated bradycardia progressing to pulseless electrical activity: case report and review of the literature. *Pharmacotherapy* 2009: 29(12): 1492.
35. Radek L, Kallionpaa RE, Karvonen M, Scheinin A, Maksimow A, Langsjo J, Kaisti K, Vahlberg T, Revonsuo A, Scheinin H, Valli K. Dreaming and awareness during dexmedetomidine- and propofol-induced unresponsiveness. *Br J Anaesth* 2018: 121(1): 260-269.
36. Houghton CM, Raghuram A, Sullivan PJ, O'Driscoll R. Pre-medication for bronchoscopy: a randomised double blind trial comparing alfentanil with midazolam. *Respir Med* 2004: 98(11): 1102-1107.
37. Oztas S, Aka Akturk U, Alpay LA, Meydan B, Ogun H, Taylan M, Yalcinsoy M, Calisir HC, Gorguner AM, Ernam D. A comparison of propofol-midazolam and midazolam alone for sedation in endobronchial ultrasound-guided transbronchial needle aspiration: a retrospective cohort study. *Clin Respir J* 2017: 11(6): 935-941.
38. Franzen D, Schneiter D, Weder W, Kohler M. Impact of sedation technique on the diagnostic accuracy of endobronchial ultrasound-guided transbronchial needle aspiration. *Endosc Ultrasound* 2017: 6(4): 257-263.
39. Conte SC, Spagnol G, Confalonieri M, Brizi B. Deep sedation versus minimal sedation during endobronchial ultrasound transbronchial needle aspiration. *Monaldi Arch Chest Dis* 2018: 88(3): 967.
40. Yarmus LB, Akulian JA, Gilbert C, Mathai SC, Sathiyamoorthy S, Sahetya S, Harris K, Gillespie C, Haas A, Feller-Kopman D, Sterman D, Lee HJ. Comparison of moderate versus deep sedation for endobronchial ultrasound transbronchial needle aspiration. *Ann Am*

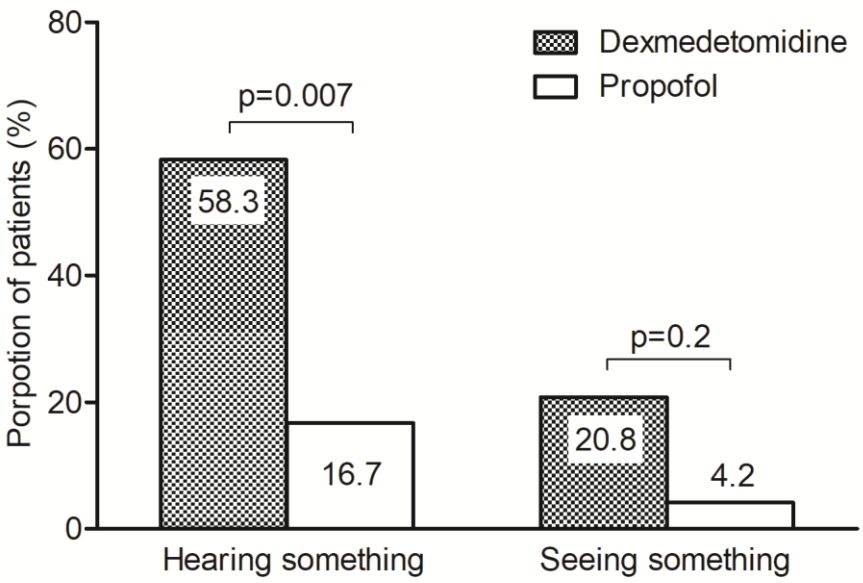
Thorac Soc 2013: 10(2): 121-126.
41. Fernandes MGO, Santos VF, Martins N, Sucena MC, Passos MM, Marques MM, Magalhaes AM, Bugalho A. Endobronchial Ultrasound under Moderate Sedation versus General Anesthesia. *J Clin Med* 2018: 7(11).

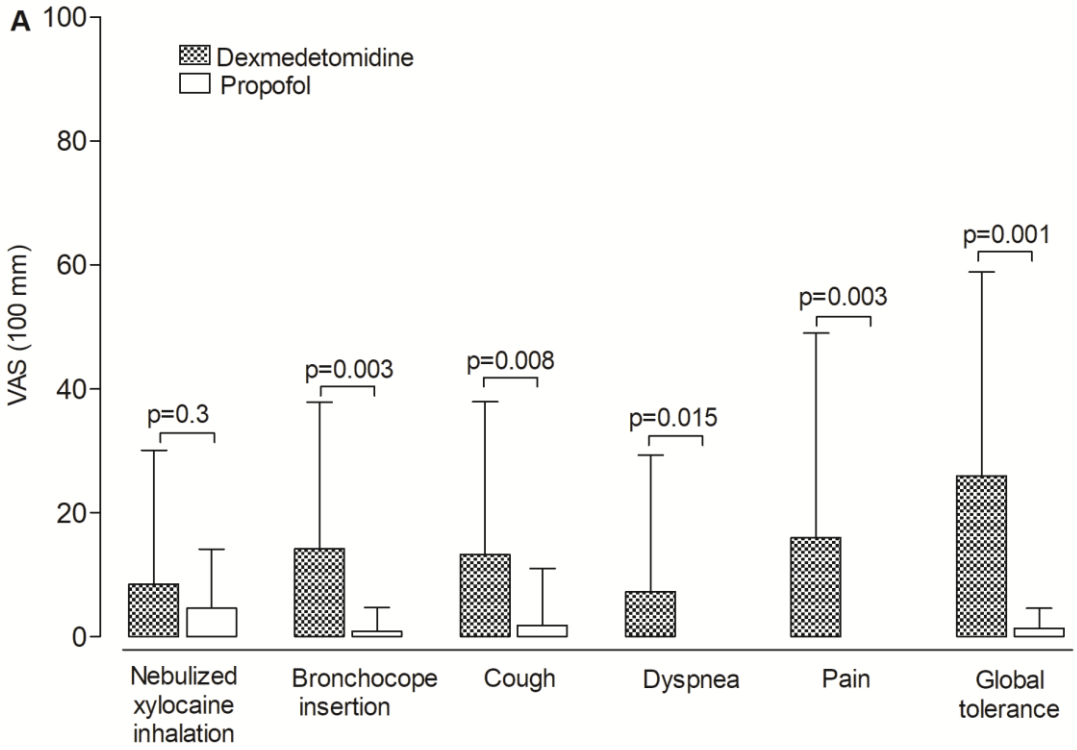
Figure legends

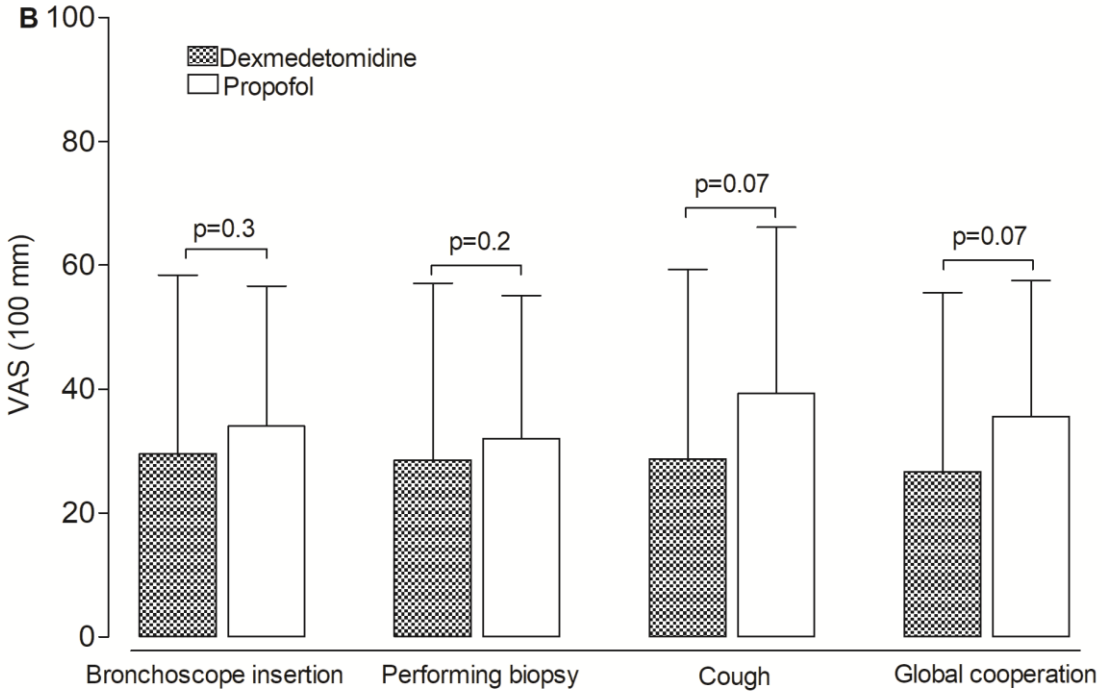
Figure 1. Wakefulness during sedation. Following recovery, patients were asked if they had seen or heard anything during the bronchoscopic procedure. One subject in each group refused to answer the questionnaire.

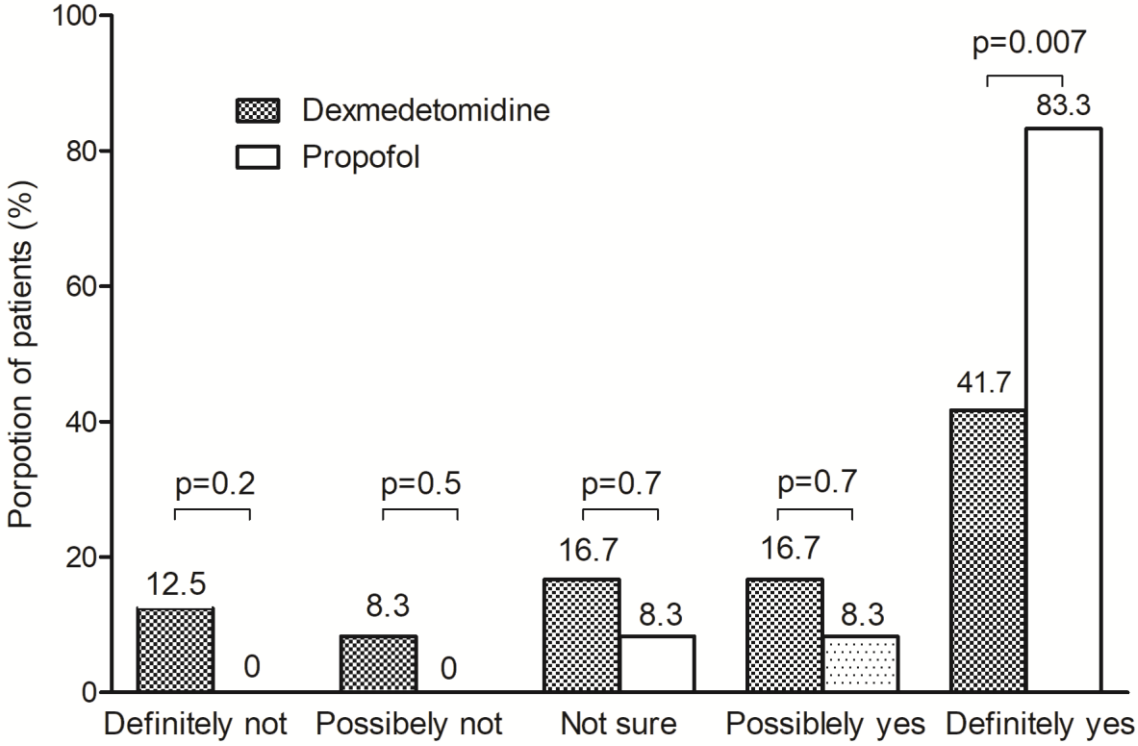
Figure 2. A: Patient tolerance for procedure-related symptoms. Following recovery, subjects answered a questionnaire on procedure-related symptoms, including reactions to nebulized xylocaine inhalation, stimulation caused by scope insertion through the mouth, coughing, dyspnea, pain, and global tolerance to the entire procedure. Note that one subject in each group refused to answer the questionnaire. **B: Patient cooperation during the bronchoscopic procedure.** Bronchoscopist answered a questionnaire on the ease of scope insertion and biopsy, coughing by the patient, and global cooperation during the procedure. The design of the questionnaire was based on a 100-mm visual analogue scale (VAS, 0: no bother, 100: worst intolerable/uncooperative).

Figure 3. Willingness to undergo repeated bronchoscopic procedure. Following recovery, patients were queried about their willingness to undergo the procedure again if indicated clinically (definitely not, possibly not, not sure, possibly yes and definitely yes). One subject in each group refused answer the questionnaire.


80
60
40
20
0
Porpotion of patients (%)
Dexmedetomidine
Propofol
p=0.007
58.3
16.7
p=0.2
20.8
4.2
Hearing something
Seeing something


A
100
80
60
40
20
0
VAS (100 mm)
Dexmedetomidine
Propofol
p=0.3
p=0.003
p=0.008
p=0.015
p=0.003
p=0.001
Nebulized xylocaine inhalation
Bronchocope insertion
Cough
Dyspnea
Pain
Global tolerance


B
100
80
60
40
20
0
VAS (100 mm)
Dexmedetomidine
Propofol
p=0.3
p=0.2
p=0.07
p=0.07
Bronchoscope insertion
Performing biopsy
Cough
Global cooperation


100
80
60
40
20
0
Porpotion of patients (%)
Dexmedetomidine
Propofol
p=0.2
p=0.5
p=0.7
p=0.7
p=0.007
12.5
0
8.3
0
16.7
8.3
16.7
8.3
41.7
83.3
Definitely not
Possibely not
Not sure
Possiblely yes
Definitely yes

Supplemental material

The interventions of the investigators in charge of sedation

In an effort to maintain SpO_2>90% (i.e., avoid hypoxemia) supplemental oxygen was administered up to 6L/min, and/or head/jaw maneuvers were performed. Ventilation assistance using a bag valve mask was also provided if indicated. Fluid resuscitation and leg elevation were used in cases of hypotension to maintain systolic blood pressure (SBP)>90 mmHg and mean arterial blood pressure (MAP)>65 mmHg.

Table S1. Baseline hemodynamics prior to sedation for bronchoscopy

	Dexmedetomidine (n= 25)	Propofol (n =25)	p value
Mean arterial pressure, mmHg	93.2 (13.9)	94.4 (14.2)	1.0
Systolic blood pressure, mmHg	132.7 (19.6)	134.2 (22.1)	1.0
heart rate, beat/min	75.1 (10.4)	74.7 (11.2)	0.9
SPO2, %	99.5 (1.0)	98.8 (2.4)	1.0
BIS level	92.7 (4.7)	93.4 (3.9)	0.9

Table S2. Hemodynamics during induction period# of sedation for bronchoscopy

Events	Dexmedetomidine (n= 25)	Propofol (n =16)	p value
Blood pressure, mmHg			
Lowest MAP	86.3 (10.6)	90.9 (14.4)	0.3
∆MAP†	-8.1 (9.6)	-3.0 (9.8)	0.06
MAP<65mmHg, n (%)	0 (0)	0 (0)	-
Lowest SBP	119.7 (14.3)	124.9 (18.8)	0.3
∆SBP*	-12.4 (15.3)	-9.3 (16.3)	0.5
SPP<90mmHg, n (%)	0 (0)	0 (0)	-
Heart rate, beat/min			
Lowest heart rate	61.9 (10.2)	69.7 (10.7)	0.03
∆heart rate*	-12.7 (7.7)	-5.0 (6.1)	<0.01
Heart rate<60/min, n (%)	10 (40.0)	4 (16.0)	0.1

Oxygenation, %			
Lowest SPO2	94.0 (18.7)	96.3 (4.9)	0.5
∆SPO2*	-5.2 (18.3)	-2.5 (3.2)	0.4
SPO2<90%, n (%)	1 (4.0)	2 (8.0)	1.0
BIS level at induction achieved	82.4 (13.1)	77.3 (9.9)	0.06
Mean BIS level during induction	89.5 (5.7)	86.1 (5.8)	0.03

Data are presented as number and percentage or mean with standard deviation.

#Induction: The 10-min period during which Dexmedetomidine was administered at 1ug/kg (study group) or propofol was administred to achieve the desired level of sedation (control group).

*∆ is defined as the difference between the lowest vital sign readings before induction and during the induction period.

Table S3. Hemodynamics during recovery period# of sedation for bronchoscopy

Events, n (%)	Dexmedetomidine (n= 25)	Propofol (n =25)	p value
Blood pressure, mmHg			
Lowest MAP	77.9 (12.3)	79.7 (15.2)	0.7
∆MAP*	-14.6 (1.3)	-14.7 (14.0)	0.8
MAP<65mmHg, n (%)	0 (0)	2 (8.0)	0.5
Lowest SBP	107.1 (15.2)	112.3 (18.9)	0.4
∆SBP*	-24.5 (17.2)	-22.0 (22.8)	0.8
SPP<90mmHg, n (%)	1 (4.0)	2 (8.0)	1.0
Heart rate, bat/min			
Lowest heart rate	65.4 (10.1)	76.6 (14.7)	0.008
∆heart rate*	-9.7 (8.9)	1.9 (11.5)	<0.001
Heart rate<60/min, n (%)	8 (32.0)	3 (12.0)	0.2

Oxygenation, %			
Lowest SPO2	95.6 (3.9)	95.4 (3.6)	0.7
∆SPO2*	-3.7 (3.8)	-3.5 (4.2)	0.9
SPO2<90%, n (%)	3 (12.0)	1 (4.0)	0.6

Duration between completion of bronchoscopy and the point at which orientation was regained.

*∆ is defined as the difference between the lowest vital sign readings before induction and during the recovery period.